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SHORT COMMUNICATION

Highlights of Abstracts on Plasma Cell Dyscrasia in the Annual Conference ISHBT (Kochi)

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Abstract Since last few years plasma cell dyscrasias have been in the hit list of research especially pertaining to its therapy and pathophysiology. India has taken a great leap as far as research in plasma cell dyscrasias is concerned. The year started with myeloma conference in New Delhi conducted by Army Hospital (R&R) and ended at Haematocon Kochi organised by team from CMC Vellore (Haematocon 2018). Haematocon 2018 provided an exceptional platform for the research on various aspects of plasma cell dyscrasias both from the country and abroad. A total of 23 abstracts were presented pertaining to plasma cell disorders; 13 original research papers, 08 case reports and 02 case series. There were a wide spectrum of papers which ranged from the discussion about morphological aspects, mimickers, clinical spectrum, life style in the setting of the disease, diagnostic modalities to management aspects and finally to progress and survival of these patients. Through this review we will summarize and analyze the key findings of the original research abstracts on diagnosis, risk stratification, clinical profile and treatment aspects of plasma cell disorders presented at the Haematocon 2018.

Keywords FISH in myeloma · Cytogenetics in myeloma · Cryopreserved grafts · Quality of life in myeloma patients · Myeloma chemotherapy · Refractory myeloma

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Introduction and Discussion

It is well said by an Oscar winning actor Michael Douglas and I quote; "Cancer didn't bring me to my knees, it brought it to my feet". Like other cancers it is an absolute truth for myeloma and therefore there is a need for a detailed discussion so that we can arrive at an early diagnosis and thus guide to correct definitive treatment. ISHBT 2018 gave an excellent platform for all these aspects.

Early diagnosis is critical and fortunately in the case of myeloma we have several diagnostic modalities. Among these ones one of the most fascinating but at times most difficult is that of a morphological diagnosis. There happens to be wide variety of morphological forms of plasma cells which may create difficulties in the diagnosis. Thus there is a need for awareness of these variants which will help in facilitation of timely diagnosis. This was highlighted by some abstracts presented in ISHBT 2018. In a paper by Shruthi et al. [1] in which they hve found plasma cells in bone marrow aspiration (BMA) resembling dysplastic megakaryocytes which on further biopsy with IHC confirmed to their plasma cell origin. Similarly Agarwal et al. [2] emphasised the role of biopsy and IHC helped in the differentiation. A similar paper by Monica et al. [3] highlighted the same aspects. It is well established fact that both MDS and AML may develop as Therapy related MDS/AML during the course of chemotherapy of Myeloma but posing as initial diagnostic difficulty is very rare in the literature. In an another paper entitled by Venkatesan et al. [4] revealed two cases on BMA resembling adenocarcinoma and clear cell carcinoma. These morphological variants have been very well described earlier by Banerjee et al. [5]. They reviewed various case reports/series and showed the myeloma confusing as poorly differentiated carcinoma, non-Hodgkin lymphoma, myeloid or monocytic

leukaemia, anaplastic carcinoma, signet ring variant resembling signet-ring cell carcinoma, small-cell type of myeloma mimicking small lymphocytic leukaemia/lymphoma/acute leukemic infiltrate, histiocytic variant resembling storage disorder, clear vacuoles in the cytoplasm mimicking a germ cell tumour or clear cell carcinoma, spindle plasma cells mimicking fibroblastic stromal response, spindle cell mesenchymal tumour, etc. They mentioned that the clue for the correct diagnosis was immunohistochemistry (IHC) using markers like CD138 together with kappa and lambda light chains demonstration. CD56 positivity is also helpful in our experience at our hospital AH (R&R) in differentiating neoplastic plasma cells in bone marrow biopsies. Leucocyte common antigen (CD45) and CD20 though negative in epithelial malignancies can sometimes be positive. CD79a is commonly positive but negative in 1/3 rd of the cases. Hence comprehensive IHC can be helpful in differentiating these cases from the mimickers.

Mott cells as we all are aware contain Russell bodies in the dilated endoplasmic reticulum. They were named after F.W Mott, who demonstrated these cells in 1901 in the monkey brains who were suffering from trypanosomiasis. Later on they were demonstrated in multiple Myeloma, leukaemias, auto immune disorders, chronic infections and gastric carcinoma associated with EBV [6]. Recently in our hospital AH (R&R) we have seen them in a case of lesihmaniasis. In ISHBT in one of the paper presented by Kundan Kumar et al. [7] the same were demonstrated in a case of Dengue.

As rightly quoted by American Physician and cardiologist Paul Dudley White: "We know from our clinical experience in the practice of medicine that in diagnosis, prognosis and treatment, the individual and his background of hereditary are just important, if not more so, as the disease itself"; recent advances in molecular studies have made significant changes in the diagnosis and risk stratification of multiple myeloma. In recent years there has been shift of focus on risk stratification in MM from the conventional metaphase cytogenetics to interphase Fluorescent in situ hybridization (iFISH), Whole exome sequencing (WES) and Gene expression profiling (GEP). Metaphase cytogenetics requires proliferating cells which the plasma cells lack hence is not a sensitive method for the detection of cytogenetic abnormalities in MM. Also, there are various cryptic translocations for which metaphase cytogenetics is not sensitive. Therefore, FISH analysis is recommended for early detection of abnormalities. Unfortunately there have been very few studies published on the cytogenetic profile of MM patients from India. A recent study by Dhiman et al. in 2016 concluded that in India an early age of presentation is an issue. Secondary mutations gets accumulated as the age advances, but if a young patient is presenting with increased severity of disease then as per author it needs exploration for additional abnormalities. They found that out of sixty eight patients of myeloma, 23 (33.82%) had one genetic abnormality out of which 13q14.3 deletion was the most frequent aberration (n = 10) (14.7%) followed by p53 absence at 17p13 in 8/68 (11.8%), 11q13 abnormality in 3/68 (4.4%), IgH (14q32) aberrations in 2/68 (2.94%) patients [8]. More than one chromosomal aberration was present in 4 patients. In a paper submitted by Janet et al. [9] the authors reviewed all 416 MM patients who were evaluated for FISH analysis from Jan 2012–July 2018. They evaluated bone marrow using one or more of the following four commercially available probes (Vysis, Abbott Molecular), namely, TP53, IgH/FGFR3, IgH/CCND1, D13S319/13q34. Plasma cell enrichment (Easy Sep, Stem Cell technologies) was done in a subset of patients (n = 80). Out of 416 patients, testing was done in 212 patients using all four probes. Overall, the most common probe used was TP53 (99%). Authors found that when they used B cell stimulated cultures, the frequencies were as follows: TP53 deletion (20/412) (4.8%), the del 13q (8/214) (3.7%), monosomy 13(13/214) (6%), t(4;14) (12/233) (5.1%)and t(11;14) (13/231) (5.6%), however the frequency of TP53 gene deletion was higher when Plasma cell enriched samples were used as compared to B-cell stimulated cultures without PC enrichment (10% vs. 5%). (TP53 gene deletion—8/80 patients, the t(4;14)—1/14 patients, t(11;14)—1/5 patients, monosomy 13—4/5 patients, with no del 13q). Thus authors have signified the role of PC enriched samples as compared to B-cell stimulated cultures. Their study showed results with some differences from another Indian study by Dhiman et al. in terms of involvement of cytogenetic abnormalities. Their study also revealed some differences in the MM patients of Indian patients as compared to western one. These included a lower median age at 56 years with range from 30 to 82 years which is almost decade younger than those from western countries.

There have been several studies concerning the expression of CD 20 and cyclin D1 in MM and its correlation with clinical, prognosis and morphological aspects. There is vast diversification in the literature as far as immunophenotypic correlation of MM is concerned. Positivity of Cyclin D1 and the CD20 and negativity of CD56 phenotypes have all previously been found to be associated with t(11;14) [10]. Study has also shown CD20 positivity association with the distribution pattern in bone marrow biopsy being most likely interstitial. A correlation between CD 20 positivity has also been mentioned between small mature plasma cells and t (11.14) in patients with MM [11].

In consideration of the above study a paper was presented by Khan et al. [12] concluded from their study that there was no statistical significance between pattern of

infiltrate and CD 20 and cyclin D1 expression. In their study diffuse pattern of infiltrate on biopsy was most common.

Bone marrow fibrosis in MM is documented but there is scarcity of literature and therefore its effect on prognosis is also limited. Authors have found in their study of 585 patients that bone marrow fibrosis was present in 38% of cases. Also on comparison of both patients with and without fibrosis patients with fibrosis had significantly worse survival (5.0 years vs. 4.4 years, respectively). This difference was significantly greater in males, young patients (< 65 years). Besides they also found that survival was worst in advanced fibrosis (4.5 years for grade 1 fibrosis, and 3.0 years for grade 2 and 3) [13]. Priya Murthy et al. [14] have found in their study that 29.62% (32/108) cases demonstrated some degree of marrow fibrosis (12 cases with grade 1 reticulin, 13 cases with grade 2 and 7 cases with grade 3 reticulin). They didn't find any significant correlation between fibrosis and plasma cell morphology. However they couldn't establish correlation between marrow fibrosis and prognosis because of lack of follow up.

Though there is a lack of literature, bleeding is still not a common presenting symptom of MM.Various studies have reported bleeding rates of 36% in MM patients [15]. M proteins inhibit specifically against coagulation factors, VWF and FVIII/platelet glycoprotein and leads to bleeding disorders. Thrombocytopenia because of bone marrow replacement, myelosuppressive effects of chemotherapy, renal/liver failure may also contribute to bleeding. Bleeding is especially much common in later stages of disease. Purohit et al. [16] presented a case report of MM with bleeding and emphasised on importance of understanding it.

In MM, median age at diagnosis is 70 years with very rare patients having age less than 30 years. Various Studies have reported similar clinical and biological characteristics on comparison in multiple myeloma among young and the elderly patients but the International Myeloma Working Group have found in their analysis a longer median survival among patients younger than 40 years by almost 54 months [17]. A case report by Muhammad et al. [18] found that their young patient died just after 3 month of Autologous transplant. Data from Asian country is limited and hence a need for a large data to see the clinical and biological pattern.

20–50% of MM patients have acute kidney injury at the time of diagnosis [19]. Aggressive supportive treatment and prompt initiation of Bortezomib-based anti-myeloma therapy are the cornerstones of management as reported by various studies [20–22].

Nath et al. [23] have reported that Bortezomib/Cyclophosphamide/Dexamethasone (CyBorD) regimen is considered to be the preferred initial induction therapy in newly diagnosed myeloma patients with acute renal insufficiency and have found that complete renal response was achieved in 94% (32/34) of their patients, including the patients who required dialysis. In their study hemodialysis was indicated in a minority of patients.

Similarly, there are many trials going on for other regimens as also shown in Table 1. As can be seen in the Table 1 progression free survival (PFS) and overall survival (OS) were significantly superior with VRD compared with Rd combination. Based on these data VRD or VTD are considered to be the preferred regimens for initial therapy in MM.

Similarly if we compare CTD versus VCD a study by Cavo et al. [25] have shown that the rates of complete response (CR), very good partial response (VGPR) or higher were significantly higher with VTD vs. VCD. However the probability to achieve less than PR was threefold lower with VTD vs. VCD. This was in concordance with the paper presented by Kumar et al. [26] reported that in the three drug regime, in patients receiving VTD, sCR/CR, VGPR and PR was achieved in 30.77%, 46.15% and 15.38% of the patients. In patients receiving VCD, sCR/CR, VGPR and PR was achieved in 18.75%, 31.25% and 31.25% of the patients. They also found that

Table 1 Results of recent randomized studies in newly diagnosed myeloma (Adapted from Ref [24])

Trial	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (median in months)	Overall survival
Facon	MPT	547	62	28	21.2	48 months (median)
	Rd till progression	535	75	44	25.5	56 months (median)
Attal et al.	VRD-ASCT					88% at 3 years
	VRD					88% at 3 years

MPT melphalan plus prednisone plus thalidomide, *Rd* lenalidomide plus dexamethasone, *VTD* bortezomib, thalidomide, dexamethasone, *VCD* bortezomib, cyclophosphamide, dexamethasone, *VRD* bortezomib, lenalidomide, dexamethasone, *ASCT* autologous stem cell transplantation, *N/A* not available, *NS* not significant, *CR* complete response, *VGPR* very good partial response

no patient on VTD experienced disease progression during induction therapy. Among the side effects peripheral neuropathy and skin rashes occurred more frequently with VTD compared to VCD [25]. However VCD was associated more commonly with severe haematological toxicity than VTD. This was in concordance of 4 years study by Ankit K. Jitani [27] who concluded that VTD was a safe and effective triplet drug regimen for newly diagnosed multiple myeloma. In another paper presented by Suvir Singh et al. from Christian Medical College, Ludhiana who concluded that there was no significant difference in 4 year OS between PI (Bortezomib) and IMiD (Thalidomide/Lenolidamide) group. This is an important finding as each month of IMiD based therapy is almost 3 times lesser in cost than Bor. Another paper presented by Nikhil M. Kumar [26] showed that among patients, who received VD, 10% achieved CR, 30% patients achieved VGPR and 50% patients achieved PR. While in the three drug regime, in patients who received VTD, sCR/CR, VGPR and PR was achieved in 30.77%, 46.15% and 15.38% of the patients. In patients who received VCD sCR/CR, VGPR and PR was achieved in 18.75%, 31.25% and 31.25% of the patients.

In refractory MM novel drugs like carfilzomib (CFZ), a new-generation proteasome inhibitors have a significant role. In a recent study [28] by Uysal et al. have reported the ORR with Carfilzomib to be 26.3% and the best response was seen in PR. They reported median duration of response rate and time to next therapy to be 8 (7–9) months and 3 (2–16) months, respectively. In their study the most common haematological side-effect were anaemia and thrombocytopenia while the most common non-haematological side effect was fatigue. Similar another study by Demopoulos et al. reported similar findings with relapsed/refractory multiple myeloma patients treated with carfilzomib and dexamethasone (median 47·6 months) had significantly longer OS than those who were treated with bortezomib and dexamethasone (40·0 months) [29]. Similar findings were observed by Sandal et al. [30] in their paper submitted with the overall response rate (ORR) by Carfilzomib was 57.1% with one patient achieving VGPR and three patients achieving PR.

As we all are aware that any autologous stem cell transplantation process starts with stem cell mobilization followed by its collection followed by administration of high dose chemotherapy with melphalan and subsequent reinfusion of the collected stem cells. Now there is a big discussion on the cards regarding the Melphalan versus other combination chemotherapy. Gay et al. [31] have reviewed that MEL200-Autologous SCT significantly prolonged PFS in comparison to bortezomib-lenalidomide-dexamethasone (VRD) (median 50 vs. 36 months; $P < 0.001$), and also in comparison to bortezomib-melphalan-prednisone (VMP). There were no increased toxic related deaths reported with MEL200-ASCT. Similarly Uday et al. [32] found that in their MEL200-Autologous SCT an overall Survival (OS) was 72% with a TRM (transplant related mortality) of 3.4%. The survival among patients with renal involvement was significantly lower (56% Vs 80%) at 2 years. They noticed that OS of the patients significantly improved with time. OS of patients who received 2 or more than 2 therapy had an extremely poor survival compared to those with a single line of therapy which was in concordance with Francesca Gay review article. Uday et al. found that 3 years Relapse Free Survival (RFS) was 66% and 5 Y RFS was 49%. Another finding was in the OS in patients with ISS 3 which was significantly lower in comparison to ISS 1.

After comparison of patients who received Melphalan versus other chemotherapy, subsequently comparison of different dosage of Melphan was also discussed in paper by Sahil Bambroo et al. from Amrita Institute of Medical Sciences who concluded that patients who received Melphalan at 200 mg/m2; oral mucositis was seen in 63.6% as compared to 57.9% cases in the Melphalan (140 mg/m2 or lesser) group. Grade 3 or more mucositis was seen only in the Melphalan 200 mg/m2 group. There was no significant difference in the median time taken for Neutrophil and Platelet recovery. Median duration of hospital stay was 26 days in Mel200 group as compared to 22 days in Mel (140 or lesser) group. Use of higher antibiotics was required in 81.8% in the Mel200 group while only 52.6% in the Mel (140 or lesser) group needed higher antibiotics. However the effect on outcomes is yet to be studied. Recent studies by Auner et al. [33] did an in-depth study and found that OS, PFS, cumulative incidence (CI) of relapse, non-relapse mortality, hematopoietic recovery and second primary malignancy rates were not significantly different between the melphalan 140 mg/m^2 and melphalan 200 mg/m^2. Also in their multivariable subgroup analysis they found that there was significant advantage of OS, PFS with melphalan 200 mg/m^2 in patients transplanted in less than partial response. However when transplantation was done in very good partial or complete response then melphalan 140 mg/m^2 was better for overall survival. They also found that there were no significant survival or relapse rate differences between melphalan 200 mg/m^2 and melphalan 140 mg/m^2 patients with age, renal function, prior proteosome inhibitor treatment, gender, Karnofsky score, high-risk, standard-risk chromosomal abnormalities.

After the stem cell collection now these cells are either cryopreserved and then infused or can be infused afresh 24–48 h after their collection. Now in developing countries this is a challenging task as cryopreservation may not be available or if available makes financial constraints to patients. A recent study by Kardduss et al. [34] along with

some other studies have shown that autologous transplantation in myeloma is possible even without cryopreservation. This has led to more wide access to financial constraint countries having limited access. A long term data was presented by Kulkarni [35] pertaining to this who concluded that the use of GCSF mobilized non-cryopreserved grafts resulted in adequate engraftment for most patients with myeloma undergoing ASCT, thus confirming the study by Kardduss et al.

Any chronic disease or its long therapy also has lots of psychological issue and effects on quality of life. This particular issue needs emphasis and analysis. This was discussed by Raghavan et al. [36] concluded that the five highest unmet needs in myeloma patients were "need to reduce stress in my life"(78%), "need to address concerns of cancer coming back"(56%), "need to handle social/-work situations"(46%), "need for emotional support"(51%) and "need to move on with my life"(51%). They found that unmet needs in myeloma patients was significantly higher when compared to that reported in western studies (26.5%) and that in cancer patients in general (40%). Similarly paper presented by Avaronnan et al. [37] concluded that in studied population there was lower health related quality of life comparison to reference population in many domains despite being on novel agents. These problems are dealt with in all developing countries and clearly show an importance of proper counselling and provision of better infrastructure.

Conclusions

The above research work presented in Haematocon 2018 highlighted the aspects of development of management of plasma cell dyscrasias in our country and abroad. If some of the challenges all over the world are same, there is some prime difference between our and developed country. Our future goals should therefore be to encourage some multicentric collaborative researches across the country so that we can aim at better management of patients and challenges related to them.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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